AMENDMENT TRANSMITTAL LETTER (Large Entity) Applicant(s): **Mark C. Noe et al.**			Docket No. **PC10491A(16319)**
Serial No. **09/635,433**	Filing Date **August 10, 2000**	Examiner **T. McKenzie**	Group Art Unit **1624**

Invention: **SELECTIVE INHIBITION OF AGGRECANASE IN OSTEOARTHRITIS TREATMENT**

TO THE COMMISSIONER FOR PATENTS:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST # PREV. PAID FOR		NUMBER EXTRA CLAIMS PRESENT	RATE	ADDITIONAL FEE
TOTAL CLAIMS	5	-	23	=	0	x $18.00	$0.00
INDEP. CLAIMS	1	-	5	=	0	x $86.00	$0.00
Multiple Dependent Claims (check if applicable) ☐							$0.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT							$0.00

☒ No additional fee is required for amendment.

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- ☒ Any additional filing fees required under 37 C.F.R. 1.16.
- ☒ Any patent application processing fees under 37 CFR 1.17.

Signature

Dated: **October 31, 2003**

Marvin Bressler
Registration No. 25,132
SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, New York 11530
516-742-4343

I certify that this document and fee is being deposited on **10/31/03** with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Marvin Bressler

Typed or Printed Name of Person Mailing Correspondence

cc:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Mark C. Noe et al.

Examiner: Thomas McKenzie

Serial No: 09/635,433

Art Unit: 1624

Filed: August 10, 2000

Docket: PC10491A (16319)

For: SELECTIVE INHIBITION OF AGGRECANASE IN OSTEOARTHRITIS TREATMENT

Dated: October 31, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE UNDER 37 C.F.R. §1.111

Sir:

This is in response to the Official Action dated October 9, 2003.

All the claims presented for examination in this application have been rejected on formal and substantive grounds. Applicants have carefully considered these grounds of rejection and respectfully submit that all the claims currently in this application are patentable over the rejection of record.

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, Virginia 22313-1450, on October 31, 2003.

Dated: October 31, 2003

Marvin Bressler

Three formal grounds of rejection are imposed in the outstanding Official Action. The first of these grounds, directed to all the claims currently in this application, Claims 16 to 20, is made under 35 U.S.C. §112, second paragraph, as being indefinite.

The specific recitation embodied in Claims 16 to 20 predicating this ground of rejection is the alleged indefiniteness introduced into Claim 16 by the wavy line in the upper right hand corner of the formula of Claim 16. Claims 17 to 20 are similarly rejected based on their ultimate dependency from Claim 16.

The Official Action avers that this wavy line introduces indefiniteness by veiling the exact chemical structure of compounds within the scope of Claim 16. The Official Action argues that dangling valences are not permitted and that an essential portion of the compound whose use is claimed is not defined.

Applicants submit that the use of a wavy line is a permissible expedient in defining a substituent bonded to the remainder of a claimed compound. In this case, Claim 16 refers to a carboxylic acid hydroxamide wherein the substituent, predicating the subject rejection, is the claimed derivative which includes the subject wavy line.

It is axiomatic that a patent application, including its claims, is required to be definite to those skilled in the art. Those skilled in the art understand the basic structure of a carboxylic acid hydroxamide. Those skilled in the art similarly appreciate that the claimed derivative, which replaces a hydrogen atom, provides the complete definition of the claimed carboxylic acid hydroxamide derivative. The inclusion of a wavy line merely means, to those skilled in the chemical arts, the rest of the molecule.

Indeed, the absence, rather than the presence, of the claimed wavy line would predicate indefiniteness. The compound claimed in the method of Claims 16 to 20 is fully

defined by the inclusion of the wavy line. This is so insofar as the wavy line, as stated above, is a short hand means of stating "the rest of the molecule." As such, the definiteness of compounds within the scope of the claims of the present application is assured. The wavy line limits the scope of compounds within the contemplation of Claims 16 to 20 to carboxylic acid hydroxamides which include the claimed substituent.

The second formal ground of rejection, again directed to Claims 16 to 20, is imposed under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Official Action avers that the rejected claims include subject matter not described in the specification in such a way as to reasonably convey, to one skilled in the art, that the inventors had possession of the claimed invention at the time the application was filed. Specifically, chemical structures of the aggrecanase inhibitors are absent therein. The Official Action argues that by beyond disclosing molecular weight, the presence of a single functional group and the required, rather than desired, pharmacological activity, applicants fail to demonstrate that they understand the structures of these molecules.

Applicants submit that this ground of rejection is unavailing. The instant formal rejection is unsustainable insofar as the aforementioned Official Action admission of recited molecular weight, functional group and desired pharmacological activity, in combination with the requirement that the functional group be a substituent of an carboxylic acid hydroxamide, establishes the adequacy of the written description in support of Claims 16 to 20.

Those skilled in the art are certainly aware of the basic structure of a carboxylic acid hydroxamide. Indeed, a representative class of carboxylic acid hydroxamides are fully described in the specification of the present application. Admittedly, the method of Claims 16

to 20 encompass all carboxylic acid hydroxamides having the specific substituent recited in those claims. However, especially in view of the exhaustive description of synthesis of the broad class of carboxylic acid hydroxamides provided in the specification of the present application, there is no question that the scope of Claims 16 to 20 is fully supported by the enabling specification of the present application.

Insofar as meeting the requirement of describing distinguishing identifying characteristics of this broad class of carboxylic acid hydroxamides, applicants emphasis that the limitations of molecular weight, the requirement of a specific single functional group and the very specific requisite pharmacological activity establish conclusively that the class of compounds within the scope of these claims are fully supported by the enabling specification of the present application.

The third formal ground of rejection is imposed under 35 U.S.C. §112, first paragraph as not providing enablement for the manufacture of all carboxylic acid hydroxamides compounds within its scope.

The Official Action admits that the compounds of Formula I are fully enabled by the specification of the present application. The class of compounds of Formula I are carboxylic acid hydroxamides having an aggrecanase inhibiting activity recited in Claim 16. The synthesis of compounds within the scope of Formula I are fully described in the specification. Indeed, the synthesis of these carboxylic acid hydroxamides are described in exhaustive detail.

When this exhaustive description is considered in conjunction with large number of working examples, which include carboxylic acid hydroxamides having aggrecanase inhibiting activity, it is clear that those skilled in the art are provided with more than adequate

information to enable them to synthesize the claimed carboxylic acid hydroxamides. Applicants submit that this detail is sufficient, given the many working examples of carboxylic acid hydroxamides having a substituent within the scope of the generic substituent set forth in Claim 16, to permit those skilled in the art to practice the method of Claims 16 to 20.

The above remarks are buttressed by the fact that the specific class of carboxylic acid hydroxamides, the class of carboxylic acid hydroxamides having an optionally substituted benzyloxyphenyl substituent, are fully described in the specification. That is, the specific class of carboxylic acid hydroxamides within the scope of the present application are fully supported by the specification. To require applicants to exhaustively include other carboxylic acid hydroxamides, which are synthesized in substantially the same manner as those within the scope of Formula I, would unduly lengthen the specification. It is for this reason that the requirements of 35 U.S.C. §112 are defined so that their requirements need be met only by those skilled in the art. Clearly, the exhaustive disclosure of synthesis routes for the manufacture of compounds of Formula I suffice to meet the requirement of enablement, under 35 U.S.C. §112, first paragraph, of Claims 16-20.

Six substantive grounds of rejection are imposed in the outstanding Official Action. The first of these, directed to all the claims currently in this application, Claims 16-20, is imposed under 35 U.S.C. §102(e) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being made unpatentable by U.S. Patent 6,576,664 to Yao et al.

The specific portion of Yao et al. that predicates this ground of rejection is the disclosure of one of the working examples described in that patent, Example 10. The compound of Example 10, at Column 66, includes a meaning of R_3 of 4-

benzyloxyphenylmethyl. The Official Action avers that that compound is a substituent within the contemplation of carboxylic acid hydroxamide derivatives recited in Claim 16. Indeed, the Official Action avers that the compound of Example 10 is a specific example of such a compound when R^5 and R^6 are hydrogen. As such, the Official Action submits that the compound employed in the method of Claim 16, from which Claims 17 to 20 ultimately depend, is within the scope of the carboxylic acid hydroxamide compounds of Claim 16.

Applicants have considered this ground of rejection and respectfully submit that none of the claims currently in this application are anticipated, under 35 U.S.C. §102(e), by Yao et al. The substituent of Claim 16 is benzyloxyphenyl. The radical R_3 in Yao et al. is distinguished from the recited substituent in that the Yao et al. compound includes an additional methylene group, e.g. $-CH_2-$, that bonds to the carboxylic acid hydroxamide.

None of the compounds within the scope of Claims 16-20 are anticipated by Yao et al. It is axiomatic that an anticipation rejection requires that each and every limitation of a claim be disclosed in a single reference. Clearly, Yao et al. does not employ any carboxylic acid hydroxamide derivative having the same substituent as that required by Claims 16-20.

The application of the rule in In re Ludtke, 58 CCPA 1159, 441 F.2d 660, 169 USPQ 563 (CCPA 1971) is not applicable to the present application. As emphasized above, it is not the functional limitation recited in the rejected claims that predicates novelty of the claimed subject matter. Rather, the distinguished nature of the compounds of the present application over those disclosed in Yao et al. definitively establishes that the teaching of Yao et al. does not inherently anticipate any of the claims of the present application.

Turning to the second substantive rejection imposed in view of Yao et al., the rejection of Claims 16 to 20, under 35 U.S.C. §103(a) as being made obvious by Yao et al., applicants

submit that Claims 16-20 all require that the method of those claims treat the medical condition of articular cartilage destruction by administering a therapeutically effective amount of a carboxylic acid hydroxamide derivative distinguished structurally from any of the compounds disclosed in Yao et al. Moreover, these carboxylic acid hydroxamide derivatives must exhibit an aggrecanase IC_{50} of less than about 20 nM, as measured by an aggrecanase chondrocyte assay. That the distinguished compounds recited in the method of Claims 16 to 20 have a pharmacological effectiveness not so much as hinted at by Yao et al. establishes the unobviousness of this method

It is emphasized that although the utility of the compounds disclosed in Yao et al. include inhibition of metalloproteinases, such as aggrecanase and TNF-C, there is no disclosure, suggestion or requirement that the compounds of Yao et al. disclosure exhibit an aggrecanase IC_{50} of less than about 20 nM. This very low concentration of aggrecanase emphasizes the important advance in the art of treating arthritic conditions. Those skilled in the pharmacological arts appreciate that the inclusion of even one additional methylene group most certainly affects the configuration of the molecule which, as those skilled in the art are aware, significantly determines pharmacological properties.

It is emphasized that the Official Action relies on Yao et al. for its disclosure of one compound out of a multiplicity of compounds set forth in that reference. It is well established that a prior art reference that discloses a generic formula encompassing a claimed composition does not provide the requisite motivation to select that composition from the vast number of possibilities thereby presented. In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). The above remarks establish that the generic formula does not so much as encompass the claims of the present application and, as such, is even more remote from the claims of the

present application than the case in which a generic disclosure actually embodies a claimed invention.

The suggestion that Yao et al., if not anticipatory, at least makes obvious the claims of the present application, in reality relies on the impermissible "obvious to try" test. The disclosure in Yao et al. employs a multiplicity of compounds which are remote from the claimed carboxylic acid hydroxamide compounds of the present application. The citation of Example 10, which is distinguished from the claimed compounds of the present application, as indicated above, would require one to vary the substituent until the aforementioned methylene group was removed from the group taught in Yao et al. at Example 1. It is axiomatic that "obviousness to try" is not to be equated with obviousness under 35 U.S.C. §103. Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990).

The second substantive ground of rejection imposed in the outstanding Official Action is again directed to all the claims currently in this application, Claims 16-20. Claims 16-20 stand rejected, under 35 U.S.C. §102(e), as being anticipated by or, in the alternative, under 35 U.S.C. §103(a), as being obvious over U.S. Patent 6,376,665 to Duan et al.

The Official Action avers that eight N-hydroxycarboxylamide compounds that also contain a benzyl ether of a phenol (sic) are taught in this reference. One of these compounds, the compound of Example 23, which has the structural formula set forth at Column 45, line 15, wherein R^1 is i-propyl, R^3 is 4-[(3,5-dimethylphenyl)methoxy]phenyl and $R^{b'}$ is methyl allegedly anticipates the carboxylic acid hydroxamides having the substituents of Claims 16-20.

The critical substituent is, of course, the radical R^3. That radical, 4-[(3,5-dimethylphenyl)methoxy]phenyl, is far removed from the substituent of Claims 16-20, benzyloxyphenyl. Indeed, that radical is much further removed from the claim substituent than is the substituent taught in Yao et al.

As stated above, the above remarks establishing the absence of anticipation by any of the compounds of Duan et al. of carboxylic acid hydroxamides derivatives employed in the method of Claims 16 to 20 of the present application eliminates any question regarding the functional limitation included in these claims. Suffice it to say, novelty is established based on the structural formula of the claimed invention over the compounds taught in Duan et al.

In regard to the rejection, under 35 U.S.C. §103(a), of Claims 16 to 20 as being obvious over Duan et al., the above remarks, directed to the traverse of the obviousness rejection over Yao et al., apply herein and need not be repeated.

The third substantive ground of rejection is directed to Claims 16-20, all the claims currently in this application, as being anticipated, under 35 U.S.C. §102(e), by U.S. Patent 6,214,870 to McClure et al.

The predicate for this rejection is Examples 6, 7 and 8, which appear at Column 35, line 24 to Column 37, line 31 of McClure et al. ('870), disclose compounds which are carboxylic acid hydroxamides having a substituent within the scope of Claims 16-20. The compounds of McClure et al. have utility in inhibiting aggrecanase.

Applicants submit that the limitation of utility in Claim 16, from which Claims 17 to 20 ultimately depend, obviates against the argument, advanced in the Official Action, that McClure et al. ('870) anticipates the claims of the present application. Clearly, there is no disclosure in McClure stating or suggesting that the compounds within its contemplation,

including those of Examples 6-8, exhibit an aggrecanase IC_{50} of less than about 20 nM when measured by an aggrecanase chondrocyte assay.

The Official Action, appreciating this fact, argues that that utility is inherent from the McClure et al. ('870) disclosure. Applicants again reiterate their previously enunciated criterion for imposition of an anticipation rejection based on inherency. When a reference is silent about an asserted inherent characteristic, such gap in the reference must be filled with recourse to intrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. This is so insofar as inherency may not be established by probabilities or possibilities. Continental Can Co. USA, Inc. v. Monsanto Co., 974 F.2d 1264, 1268-1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). As such, the rejection under 35 U.S.C. §102(e) is not sustainable.

The fourth substantive ground of rejection is imposed under 35 U.S.C. §102(e) as being anticipated by U.S. Patent 6,329,397 to McClure et al.

The Official Action, in applying this ground of rejection, points particularly to Example 41, at Column 71-72 of McClure et al. ('397). The Official Action indicates that other anticipatory compounds are found throughout Tables 1 to 4. These compounds are recited to inhibit aggrecanase. However, the Official Action admits that McClure et al. ('397) makes no disclosure or claim that any of the compounds within its contemplation exhibit an aggrecanase IC_{50} of less than about 20 nM.

Applicants need not reiterate their arguments in regard to the requirement of evidence establishing anticipation based on inherency. Suffice it to say, applicants' argument, supra, directed to the patentability of Claims 16-20 over McClure et al. ('870), apply with equal

weight to the patentability of Claims 16-20 over the presently discussed reference, McClure et al. ('397).

The fifth substantive ground of rejection is a judicially created obviousness-type double patenting rejection over Claim 30 of U.S. Patent 6,214,870 to McClure et al. ('870).

Claim 30 of McClure et al. ('870) is a method claim for treating any of the conditions recited set forth in the Markush group of that claim. Among these conditions is arthritis, including osteoarthritis and rheumatoid arthritis. Claim 30 recites a method administering to a mammal an amount of a compound of Claim 1 effective in treating this condition. Claim 1 recites a generic class of compounds wherein the radical Q allegedly includes the derivative recited in Claim 16 of the present application.

Suffice it to say, the definition of radicals within the scope of Q includes an incredible number of meanings including C_6-C_{10} aryl optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or more substituents per ring independently selected from fluoro, chloro, bromo, C_1-C_6 alkyl, C_1-C_6 alkoxy, perfluoro C_1-C_3 alkyl, perfluoro C_1-C_3 alkoxy and C_6-C_{10} aryloxy. Somewhere in that disclosure resides the claimed derivative of Claim 16.

Claim 30 of McClure et al. ('870), as summarized above, discloses the treatment of arthritis with a generic compound encompassing thousands of species. That disclosure, at best, discloses a broad generic class of compounds which may encompass the relatively small number of compounds within the scope of Claims 16 to 20. The disclosure of Claim 30 generally recites a utility no more specific than that the generic class of compounds of Claim 1 are useful in the treatment of arthritis, among a multiplicity of ailments. There is

no disclosure of the specific utility of aggrecanase inhibition, let alone the specific claimed aggrecanase level required in all the claims subject to this ground of rejection.

With these facts in mind, one must look to the case law which holds that this set of facts obviates against a rejection predicated upon obviousness. The case law holds that a prima case of unpatentability is not made out by a disclosure of a generic formula encompassing a vast number of species. Baird, ibid. Thus, Claim 30 of McClure et al. ('870) does not create a prima facie case of obviousness. Thus, the instant judicially created ground of rejection is without merit.

The sixth and last substantive ground of rejection is another judicially created doctrine of obviousness-type double patenting rejection. Specifically, this rejection relies upon Claim 68 of U.S. Patent 6,329,397 to McClure et al.

Claim 68 of McClure et al. ('387) is another method of treating a multiplicity of conditions, which includes arthritis, by administering to a mammal an amount of a compound of Claim 1 of McClure et al. ('387) or a pharmaceutically acceptable salt thereof effective in treating those conditions. Claim 1 recites a generic class of compounds which encompasses literally thousands of compounds in which it is assumed that the derivative of Claim 16 is disclosed somewhere in the radicals having the meaning Ar.

Applicants do not attempt to venture a guess as to which of the meanings of Ar, which is defined by language spanning almost two columns, is applied in the rejection of Claims 16-20. Suffice it to say, the above remarks, which emphasize the impossibly large number of compounds within the contemplation of this claim, as well as the absence in this claim of any hint of the effectiveness of the claimed compounds of Claims 16 to 20, wherein inhibition of aggrecanase at the level recited is required, establish that Claim 68 of McClure et al. ('387)

does create a prima facie case of obviousness for the same reasons advanced in the traverse of the obviousness type double patenting rejection over McClure et al. ('870).

The above extensive remarks establish that all the grounds of rejection imposed in the outstanding Official Action do not make unpatentable any of the claims currently in this application. Reconsideration and removal of these grounds of rejection are therefore deemed appropriate. Such action is respectfully urged.

The above remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 16-20, is therefore respectfully solicited.

Respectfully submitted,

Marvin Bressler
Registration No. 25,132
Attorney for Applicants

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
516-742-4343
MB:ml